IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

MEDPOINTE HEALTHCARE INC., Plaintiff, vs. APOTEX INC. and APOTEX CORP., Defendants.	Civil Action No. _____

COMPLAINT

Plaintiff MedPointe Healthcare Inc., for its Complaint against Defendants Apotex Inc. and Apotex Corp., hereby alleges as follows.

PARTIES

1. Plaintiff MedPointe Healthcare Inc. ("MedPointe") is a Delaware corporation having a place of business at 265 Davidson Avenue, Somerset, New Jersey 08873.

2. Upon information and belief, Defendant Apotex Inc. is a corporation organized and existing under the laws of Canada, having a place of business at 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2.

3. Upon information and belief, Defendant Apotex Inc. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

4. Upon information and belief, Defendant Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326.

5. Upon information and belief, Apotex Corp. is the United States agent for Apotex Inc. for purposes including, but not limited to, making regulatory submissions to the United States Food and Drug Administration ("FDA").

6. Upon information and belief, Apotex Corp. is the United States marketing and sales agent for Apotex Inc. wherein, following FDA approval of an Abbreviated New Drug Application ("ANDA"), Apotex Inc. manufactures and supplies the approved generic drug products to Apotex Corp., which then markets and sells those products throughout the United States, including in this judicial district.

7. Upon information and belief, and consistent with its practice with respect to other generic products, Apotex Inc. will sell the generic product accused of infringement in this Complaint through Apotex Corp. throughout the United States, including in this judicial district, following any FDA approval.

8. Upon information and belief, Apotex Corp. is the United States subsidiary and alter ego of Apotex Inc. Upon information and belief, for all purposes relevant to this action, Apotex Inc. and Apotex Corp. are effectively the same entity and are referred to collectively hereinafter as Apotex.

NATURE OF THE ACTION

9. This is a civil action for the infringement of United States Patent No. 5,164,194 ("the '194 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. §100 *et seq.*

JURISDICTION AND VENUE

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over Apotex Corp. by virtue of, *inter alia*, the fact that Apotex Corp. is a Delaware corporation.

12. This Court has personal jurisdiction over Apotex Inc. by virtue of, *inter alia*: (1) its presence in Delaware through its United States subsidiary and alter ego, Apotex Corp., which is a Delaware corporation; (2) its systematic and continuous contacts with Delaware, including its contacts with its United States subsidiary and alter ego and that entity's substantial and ongoing sale of numerous generic drugs in Delaware; (3) its performance of acts, either directly or through an agent, that have caused tortious injury in Delaware in connection with a persistent course of conduct with its United States subsidiary and alter ego; (4) its consent to personal jurisdiction in this Court in connection with another action for infringement of the '194 patent, Civil Action No. 06-164-SLR.

13. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b), (c) and (d) and 1400(b).

THE PATENT

14. On November 17, 1992, the '194 patent, titled "Azelastine Containing Medicaments," was duly and legally issued to Asta Pharma AG as assignee. Since August 16, 2002, MedPointe has been, and continues to be, the sole owner of the '194 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '194 patent is attached hereto as Exhibit A.

ACTS GIVING RISE TO THIS ACTION

15. Upon information and belief, on or about December 13, 2006, Apotex submitted ANDA 78-621 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)).

16. ANDA 78-621 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of a generic ophthalmic solution product containing 0.05% azelastine hydrochloride in an aqueous solution for use in treating, *inter alia*, seasonal allergic rhinitis ("the Generic Product"). ANDA 78-621 specifically seeks FDA approval to market the Generic Product prior to the expiration of the '194 patent.

17. ANDA 78-621 contains an allegation under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '194 patent are either invalid, unenforceable and/or not infringed by the manufacture, use or sale of the Generic Product. MedPointe received written notification of ANDA 78-621 and its § 505(j)(2)(A)(vii)(IV) allegation on March 14, 2007.

18. Upon information and belief, and consistent with its practice with respect to other generic products, Apotex Inc. has designated Apotex Corp. as its agent in the United States for purposes of filing ANDA 78-621 and for marketing and selling the Generic Product in the United States upon any approval of ANDA 78-621.

19. Apotex's submission of ANDA 78-621 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '194 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Apotex commercially makes, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States,

or induces or contributes to any such conduct during the term of the '194 patent, it would further infringe the '194 patent under 35 U.S.C. § 271 (a), (b) and/or (c).

20. Even if Apotex Inc. and Apotex Corp. are not treated as a single entity for purposes of this action, which they should be, each of them is nonetheless jointly and severally liable for the infringement of the '194 patent.

21. Apotex Inc. is jointly and severally liable for the infringement of the '194 patent. This is so because, upon information and belief, Apotex Inc. submitted ANDA 78-621 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) and will, *inter alia*, manufacture, offer to sell and sell the Generic Product upon receipt of any FDA approval of ANDA 78-621.

22. Apotex Inc.'s submission of ANDA 78-621 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '194 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Apotex Inc. commercially makes, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States, or induces or contributes to any such conduct during the term of the '194 patent, it would further infringe the '194 patent under 35 U.S.C. § 271 (a), (b) and/or (c).

23. Apotex Corp. is jointly and severally liable for the infringement of the '194 patent, regardless of which Apotex entity actually filed ANDA 78-621 and regardless of whether it is treated as the alter ego of Apotex Inc. for purposes of this action. This is so because, upon information and belief, Apotex Corp. participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-621 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA and will, *inter alia*, offer to sell and sell the Generic Product within the United States and this judicial district upon receipt of any FDA approval of ANDA 78-621.

24. Apotex Corp.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-621 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '194 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Apotex Corp. commercially makes, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States, or induces or contributes to any such conduct during the term of the '194 patent, it would further infringe the '194 patent under 35 U.S.C. § 271 (a), (b) and/or (c).

25. Apotex had actual and constructive notice of the '194 patent prior to filing ANDA 78-621.

26. MedPointe will be irreparably harmed by Apotex's infringing activities unless those activities are enjoined by this Court. MedPointe does not have an adequate remedy at law. Both the balance of the hardships as between MedPointe and Apotex and the public interest further support this Court enjoining Apotex's infringing activities.

PRAYER FOR RELIEF

WHEREFORE, MedPointe prays for judgment as follows:

A. That Apotex has infringed the '194 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA 78-621 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration date of the '194 patent, including any extensions;

C. That Apotex, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from making, using, offering to sell or selling the Generic Product within

the United States, or importing the Generic Product into the United States, prior to the expiration of the '194 patent, including any extensions;

D. That MedPointe be awarded monetary relief if Apotex commercially makes, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States, prior to the expiration of the '194 patent, including any extensions, and that any such monetary relief be awarded to MedPointe with prejudgment interest;

E. That MedPointe be awarded the attorney fees, costs and expenses that it incurs prosecuting this action under 35 U.S.C. §285; and

F. That MedPointe be awarded such other and further relief as this Court deems just and proper.

Frederick L. Cottrell, III (#2555)
Jameson A.L. Tweedie (#4927)
RICHARDS, LAYTON & FINGER P.A.
One Rodney Square
P.O. Box 551
Wilmington, Delaware 19899
(302) 651-7700
cottrell@rlf.com
tweedie@rlf.com
Attorneys for Plaintiff
MedPointe Healthcare Inc.

Of Counsel:

John M. Desmarais
Peter J. Armenio
Anne S. Toker
KIRKLAND & ELLIS LLP
Citigroup Center
153 East 53rd Street
New York, New York 10022
(212) 446-4800

Dated: April 17, 2007

EXHIBIT A

US005164194A

United States Patent [19]

Hettche

[11] Patent Number: 5,164,194

[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING MEDICAMENTS

[75] Inventor: Helmut Hettche, Dietzenbach, Fed. Rep. of Germany

[73] Assignee: Asta Pharma AG, Fed. Rep. of Germany

[21] Appl No.: 551,644

[22] Filed: Jul. 12, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov. 9, 1988, abandoned.

[30] Foreign Application Priority Data

Nov. 13, 1987 [DE] Fed. Rep. of Germany 3738681

[51] Int. Cl.[5] A61K 9/14; A61K 31/55

[52] U.S. Cl. 424/489; 424/43; 424/45; 424/464; 424/422; 514/212

[58] Field of Search 424/43, 464, 422, 45, 424/489; 514/212; 222/394; 141/24; 239/302; 248/108

[56] References Cited

U.S. PATENT DOCUMENTS

158,564	1/1875	Barnes	141/24
2,119,643	6/1938	Mendl	222/394
2,136,940	11/1938	Ehbrecht	222/394
2,457,024	12/1948	Arp	248/108
2,995,308	8/1961	Ashkenez	239/302
3,813,384	5/1974	Vogelsang	546/133
4,704,387	11/1987	Engel et al.	514/212
4,769,369	9/1988	Thomas et al	514/234 5

FOREIGN PATENT DOCUMENTS

2164058	7/1972	Fed. Rep. of Germany	546/133
3530793	3/1986	Fed. Rep. of Germany	514/212
1377231	1/1972	United Kingdom	

OTHER PUBLICATIONS

Negwer, Organic-Chemicals, Drugs and Their Synonyms, vol. II, (1987) p. 1145.

European Search Report.

Org.-Chem. drugs and their synonyms, vol. III, No. 6496 (1987).

Arzneimittel, Fortschritte 1972-1985, pp. 936 and 939 (1977).

Primary Examiner—Thurman K. Page
Assistant Examiner—Neil S. Levy
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] ABSTRACT

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings

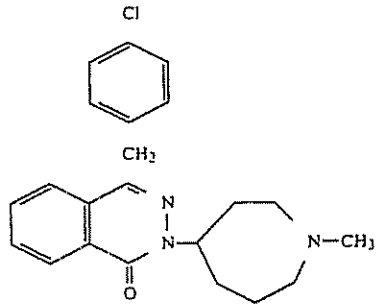
AZELASTINE CONTAINING MEDICAMENTS

This is a continuation of application Ser. No. 07/268,72, filed Nov. 9, 1988, now abandoned.

The present invention relates to the treatment of nasal and eye tissues with azelastine.

BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058

SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : 706. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It wa surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

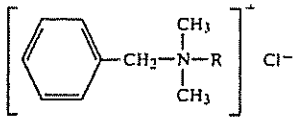
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight) Preferred preserva-

tives among the quaternary ammonium compounds are, however. alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which $R=C_{12}H_{25}$ "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present-as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thimero sal 0.002–0.02%;

benzalkonium chlorie 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric/nitrate, borate, acetate 0.002–0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05–0.15, preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/-weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight-/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine +auxiliary substances) should not exceed 30 μm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 μm.

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples

EXAMPLE 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, 68 g of sodium chloride, 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogen-phosphate. 12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]

[1] Commercially available product, for example methocel E4M premium.

The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

EXAMPLE 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80° C.). Subsequently, a solution heated to 70° C. of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester in 51.021 kg of purified water are emulsified with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

[2] Polyoxyethylene-40-stearate, solid, white to cream-colored mass, D^{25} ca. 1.1, F 40°-44° C. Solidification point ca. 41° C.

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

EXAMPLE 3

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about −55° C. in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at −55° C. 0.0688 kg of micronized azelastine hydrochloride and 0.0688 kg of micron-

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26-88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate 2 H_2O and 21 g of disodium hydrogen phosphate 2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/-weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO.	:	5,164,194
ISSUED	:	November 17, 1992
INVENTOR(S)	:	Helmut Hettche
PATENT OWNER	:	Asta Medica, AG

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

349 days

from November 17, 2009, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 27th day of February 1998.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and

JS 44 (Rev 11/04)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
MedPointe Healthcare, Inc.

(b) County of Residence of First Listed Plaintiff New Castle
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Frederick L. Cottrell, III
Jameson A. L. Tweedie
Richards, Layton & Finger
One Rodney Square
920 North King Street
Wilmington, DE 19801
302-651-7700

DEFENDANTS
Apotex Inc. and Apotex Corp.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ■ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholder's Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Eject
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth In Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ■ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reappointment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

■ Original Proceeding | ☐ 2 Removed from State Court | ☐ 3 Remanded from Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Transferred from another district (specify) | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Justice

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing (**Do not cite jurisdictional statues unless diversity**):
Action for patent infringement under 35 U.S.C. § 100 et. *seq.*
Brief description of cause: Action for patent infringement and injunctive relief

VII. REQUESTED IN COMPLAINT
☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23
DEMAND $
CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Chief Judge Sue L. Robinson DOCKET NUMBER C.A. No. 06-164-SLR

DATE April 17, 2007 SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY
RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44
Authority For Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed The attorney filing a case should complete the form as follows:

I. **(a) Plaintiffs - Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title

(b) County of Residence For each civil case filed, except U S plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing In U S plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved)

(c) Attorneys Enter firm name, address, telephone number, and attorney of record If there are several attorneys, list them on an attachment, noting in this section "(see attachment)"

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8 (a), F R C P , which requires that jurisdictions be shown in pleadings Place an "X" in one of the boxes If there is more than one basis of jurisdiction, precedence is given in the order shown below

United States plaintiff (1) Jurisdiction is based on 28 U S C 1345 and 1348 Suits by agencies and officers of the United States are included here

United States defendant (2) When the plaintiff is suing the United States, its officers or agencies, place an X in this box

Federal question (3) This refers to suits under 28 U S C 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States In cases where the U S is a party, the U S plaintiff or defendant code takes precedence, and box 1 or 2 should be marked

Diversity of citizenship (4) This refers to suits under 28 U S C 1332, where parties are citizens of different states When Box 4 is checked, the citizenship of the different parties must be checked (See Section III below; federal question actions take precedence over diversity cases)

III. **Residence (citizenship) of Principal Parties**. This section of the JS-44 is to be completed if diversity of citizenship was indicated above Mark this section for each principal party

IV. **Cause of Action**. Report the civil statute directly related to the cause of action and give a brief description of the cause

V. **Nature of Suit**. Place an "X" in the appropriate box If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive

VI. **Origin.** Place an "X" in one of the seven boxes

Original Proceedings (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U S C , Section 1441 When the petition for removal is granted, check this box

Remanded from Appellate Court (3) Check this box for cases remanded to the district court for further action Use the date of remand as the filing date

Reinstated or Reopened (4) Check this box for cases reinstated or reopened in the district court Use the reopening date as the filing date

Transferred from Another District (5) For cases transferred under Title 28 U S C Section 1404(a) Do not use this for within district transfers or multidistrict litigation transfers

Multidistrict Litigation (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U S C Section 1407 When this box is checked, do not check (5) above

Appeal to District Judge from Magistrate Judgment (7) Check this box for an appeal from a magistrate's decision

VII. **Requested in Complaint**. Class Action Place an "X" in this box if you are filing a class action under Rule 23, F R C P

Demand In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction

Jury Demand Check the appropriate box to indicate whether or not a jury is being demanded

VIII. **Related Cases.** This section of the JS-44 is used to reference relating pending cases if any If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases

Date and Attorney Signature. Date and sign the civil cover sheet
(rev 07/89)

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 07-204

cc scanned

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 3 COPIES OF AO FORM 85.

APR 17 2007
(Date forms issued)

(Signature of Party or their Representative)

Matthew Latchford
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action